Form PTO 1390 (REV 5-93) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE		ATTORNEY'S DOCKET NUMBER P32158
TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED / ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371		U.S. APPLICATION NO. (If known, see 37 C.F.R. 1.5) 09/806877
INTERNATIONAL APPLICATION NO. PCT/EP99/07416	INTERNATIONAL FILING DATE 04 October 1999	PRIORITY DATE CLAIMED 09 October 1998
TITLE OF INVENTION 7-ALKOXYCOUMARINS AS CYP2C9 SUBSTRATES		
APPLICANT(S) FOR DO/EO/US BAMBAL, Ramesh B.; ELLIOTT, Richard Leonard		

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1 [x] This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.

2. [ ] This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.

3. [x] This express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1).

4. [x] A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.

5. [x] A copy of the International Application as filed (35 U.S.C. 371(c)(2))
   a. [ ] is transmitted herewith (required only if not transmitted by the International Bureau).
   b. [x] has been transmitted by the International Bureau.
   c. [ ] is not required, as the application was filed in the United States Receiving Office (RO/US).

6. [ ] A translation of the International Application into English (35 U.S.C. 371(c)(2)).

7. [x] Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3))
   a. [ ] are transmitted herewith (required only if not transmitted by the International Bureau).
   b. [ ] have been transmitted by the International Bureau.
   c. [ ] have not been made; however, the time limit for making such amendments has NOT expired.
   d. [x] have not been made and will not be made.

8. [ ] A translation of the amendments to the claims under PCT Article 19 (35 U.S. C. 371(c)(3)).

9. [ ] An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).

10. [ ] A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11. to 16. below concern other document(s) or information included:

11. [x] An Information Disclosure Statement under 37 C.F.R. 1.97 and 1.98; and Form PTO-1449.

12. [ ] An assignment document for recording. A separate cover sheet in compliance with 37 C.F.R. 3.28 and 3.31 is included.

13. [x] A FIRST preliminary amendment.

14. [ ] A SECOND or SUBSEQUENT preliminary amendment.

15. [ ] Please amend the specification by inserting before the first line the sentence: This is a 371 of International Application PCT/EP99/07416, filed October 4, 1999, which claims benefit from the following Provisional Applications.

16. [ ] A substitute specification.

17. [ ] A change of power of attorney and/or address letter.

18. [ ] An Abstract on a separate sheet of paper.

19. [ ] Other items or information:

US APPLICATION NO. (If known see 37 CFR 1.50) 09/806877	INTERNATIONAL APPLICATION NO. PCT/EP99/07416	ATTORNEYS DOCKET NO. P32158

20. [X] The following fees are submitted:	CALCULATIONS	PTO USE ONLY
Basic National Fee (37 C.F.R. 1.492(a)(1)-(5)):		
Search Report has been prepared by the EPO or JPO $860.00	860.00	
International Preliminary Examination Fee paid to USPTO (37 CFR 1.482) $690.00		
No International Preliminary Examination Fee paid to USPTO (37 CFR 1.482) but international search fee paid to USPTO (37 CFR 1.445(a)(2)) $710.00		
Neither International Preliminary Examination Fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO.....$1,000.00		
International Preliminary Examination Fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(2)-(4).....$100.00		
ENTER APPROPRIATE BASIC FEE AMOUNT =	$860.00	
Surcharge of **$130.00** for furnishing the oath or declaration later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492(e)).	$0.00	

Claims	Number Filed	Number Extra	Rate		
Total claims	11 - 20 =	0	0 x $18.00	$0.00	
Independent claims	1- 3 =	0	0 x $80.00	$0.00	
Multiple dependent claims (if applicable)			+ $270.00	$0.00	
TOTAL OF ABOVE CALCULATIONS =				$0.00	
Reduction by 1/2 for filing by small entity, if applicable. Verified Small Entity statement must also be filed. (Note 37 CFR 1.9, 1.27, 1.28).				$	
SUBTOTAL =				$0.00	
Processing fee of **$130.00** for furnishing the English translation later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492(f)) +				$	
TOTAL NATIONAL FEE =				$860.00	
				Amount to be refunded	$
				charged	$860.00

a. ☐ A check in the amount of $____ to cover the above fees is enclosed.

b. ☒ Please charge my Deposit Account No. 19-2570 in the amount of **$860.00** to cover the above fees. A duplicate copy of this sheet is enclosed.

c. ☒ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 19-2570 . A duplicate copy of this sheet is enclosed.

d. ☒ General Authorization to charge any and all fees under 37 CFR 1.16 or 1.17, including petitions for extension of time relating to this application (37 CFR 1.136 (a)(3)).

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

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Attorney Docket No: P32158

IN THE UNITED STATES INTERNATIONAL EXAMINING AUTHORITY

International Application No.:	PCT/EP99/07416
International Filing Date:	04 October 1999
Priority Date Claimed:	09 October 1998
Applicant for DO/US:	Bambal, et al.
Title of Invention:	7-ALKOXYCOUMARINS AS CYP2C9 SUBSTRATES

Assistant Commissioner of Patents
Box PCT
Washington D.C. 20231

PRELIMINARY AMENDMENT

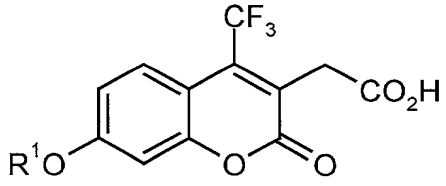
Sir:

Preliminary to calculating filing fees and examining this application, please amend the application as follows:

IN THE CLAIMS:

Please cancel claims 1-9 and replace with new claims 10-20 as follows:

--10. An assay for testing for inhibitors of the enzyme CYP2C9 which comprises contacting the enzyme and a compound of formula (I):



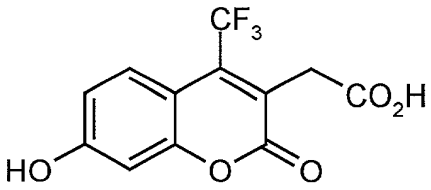
(I)

wherein R^1 represents C_{1-2}alkyl, with a test compound and measuring inhibition of O-dealkylation of the compound of formula (I) by the enzyme.

11. The assay according to claim 10 wherein R^1 is methyl.

12. The assay according to claim 10 wherein inhibition of

O-dealkylation of the compound of formula (I) by the enzyme is measured by quantifying the compound of formula (II):



(II)

13. The assay according to claim 12 wherein the compound of formula (II) is quantified by fluorescence detection.

14. The assay according to claim 13 wherein the compound of formula (II) is quantified by scanning at excitation wavelength of 410 nm and an emission wavelength of 510 nm.

15. A compound of formula (I) as defined in claim 10.

16. A process for the production of a compound of formula (I) as defined in claim 13 which comprises:

a) reaction of resorcinol and a dialkyl trifluoroacetosuccinate wherein the alkyl groups are independently selected from C_{1-2} alkyl, in the presence of polyphosphoric acid;

b) reaction of the resulting 7-hydroxycoumarin with a compound of formula R^1Hal, wherein R^1 is C_{1-2} alkyl and Hal is halogen, e.g. iodine or bromine; and

c) ester hydrolysis to give the acid of formula (I).

17. A compound of formula (II) as defined in claim 12.

18. A process for the production of a compound of formula (II) as defined in claim 12 which comprises:

a) reaction of resorcinol and a dialkyl trifluoroacetosuccinate wherein the alkyl groups are independently selected from C_{1-2} alkyl, in the presence of polyphosphoric acid; and

b) ester hydrolysis to give the acid of formula (II).

19. A method for reducing the CYP2C9 enzyme inhibitory activity of a compound, comprising the steps of identifying the compound as an inhibitor of CYP2C9 in an assay according to claim 10; and thereafter producing a chemically modified version of the test compound in which the functionality suspected to be responsible for CYP2C9 inhibition is eliminated or changed.

20. A novel compound produced according to the method of claim 19.--.

REMARKS

This Preliminary Amendment is being made upon entry of International Application No. PCT/EP99/07416 into the U.S. national phase of prosecution. Claims 1-9 have been deleted and new claims 10-20 have been added to replace the original claims, and to place the claims into proper U.S. format.

In view of the foregoing, favorable consideration of claims 10-20 are respectfully solicited.

Respectfully submitted,

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

This amendment deleted all of the previous claims and added a new set. As such, a marked up version of previous claims are not required.

EXPRESS MAIL LABEL NO. EL421189[illegible]US JC02 Rec'd PCT/PTO 05 APR 2001

Attorney Docket No. P32158

INTERNATIONAL APP. NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/EP99/07416	04 October 1999	09 October 1998

TITLE OF INVENTION
7-ALKOXYCOUMARINS AS CYP2C9 SUBSTRATES

APPLICANT(S) FOR DO/US
BAMBAL, Ramesh B.; ELLIOTT, Richard Leonard

FILING OF AN INFORMATION DISCLOSURE STATEMENT

Applicants request that the references identified on Form PTO-1449 appended hereto be considered by the Examiner and officially made of record in accordance with the provisions of 37 CFR 1.97

[X] A copy of the International Search Report, which issued on International Application No. PCT/EP99/07416 is submitted herewith. All of the publications cited in the International Search Report are listed on the attached form PTO-1449 and Applicants understand that copies have been supplied to the U.S. Patent Office by the International Bureau.

[ ] Copies of references not listed on the International Search Report are enclosed.

The attached list of citations on PTO Form 1449 is being submitted under the provisions of 37 CFR §1.56 and §1.97 in order to comply with the duty of disclosure. Their inclusion herein should not, however, be construed as an admission that any particular cited reference is effective prior art or that it discloses or renders obvious any aspect of the claimed invention. This statement is being filed within the time period specified in 37 CFR §1.97(b). No fee is required.

Respectfully submitted,

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PCT/EP99/07416

7-ALKOXYCOUMARINS AS CYP2C9 SUBSTRATES

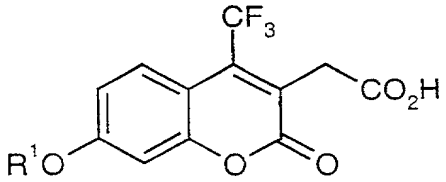
This invention relates to compounds, processes for preparing them and their use as enzyme substrates.

The majority of metabolism based drug interactions are a result of inhibition of cytochrome P450 enzymes. Drug interactions involving individual P450 enzymes can be predicted using *in vitro* methods. Typical *in vitro* P450 enzyme assays involve incubation of an appropriate substrate with a source of enzyme. Traditionally, time consuming chromatographic methods have been used for metabolite detection in these incubations. More recently the availability of fluorimetric plate readers has facilitated the higher throughput of enzyme assays in general. Adapting P450 assays to fluorescent plate reader technology requires the identification of substrates with appropriate fluorescent products for individual enzymes. Among the xenobiotic-metabolising cytochromes P450, CYP2C9 is one of those commonly responsible for the metabolism of drugs.

3-Cyano-7-ethoxycoumarin has been described for high throughput CYP2C9 inhibition screening (Crespi *et al*, *Anal. Biochem.*, 1997; 248, 188-190). However, the rate of 3-cyano-7-ethoxycoumarin metabolism by CYP2C9 is low and the extent of 3-cyano-7-ethoxycoumarin O-dealkylase inhibition does not always correlate well with a solid-phase extraction assay for CYP2C9, thus 3-cyano-7-ethoxycoumarin is not suitable for high throughput screening.

Certain compounds have now been identified which are improved substrates for CYP2C9 and which are of use for configuring high throughput inhibition screening assays.

According to the present invention there is provided an assay for testing for inhibitors of the enzyme CYP2C9 which comprises contacting the enzyme and a compound of formula (I):



(I)

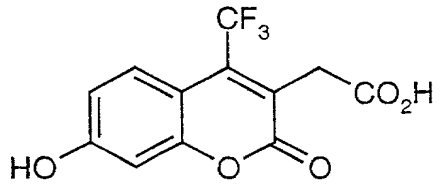
wherein R^1 represents C_{1-2}alkyl, with a test compound and measuring inhibition of O-dealkylation of the compound of formula (I) by the enzyme.

In a preferred aspect of the invention R^1 is methyl.

Generally the rate of O-dealkylation of the compound of formula (I) in the absence of test compound will be known, as will the extent of O-dealkylation at given time points.

The assay may test for inhibition of O-dealkylation continuously or at specified time points.

O-Dealkylation of the compound of formula (I) following incubation with CYP2C9 gives a readily quantifiable fluorescent product of formula (II):



(II)

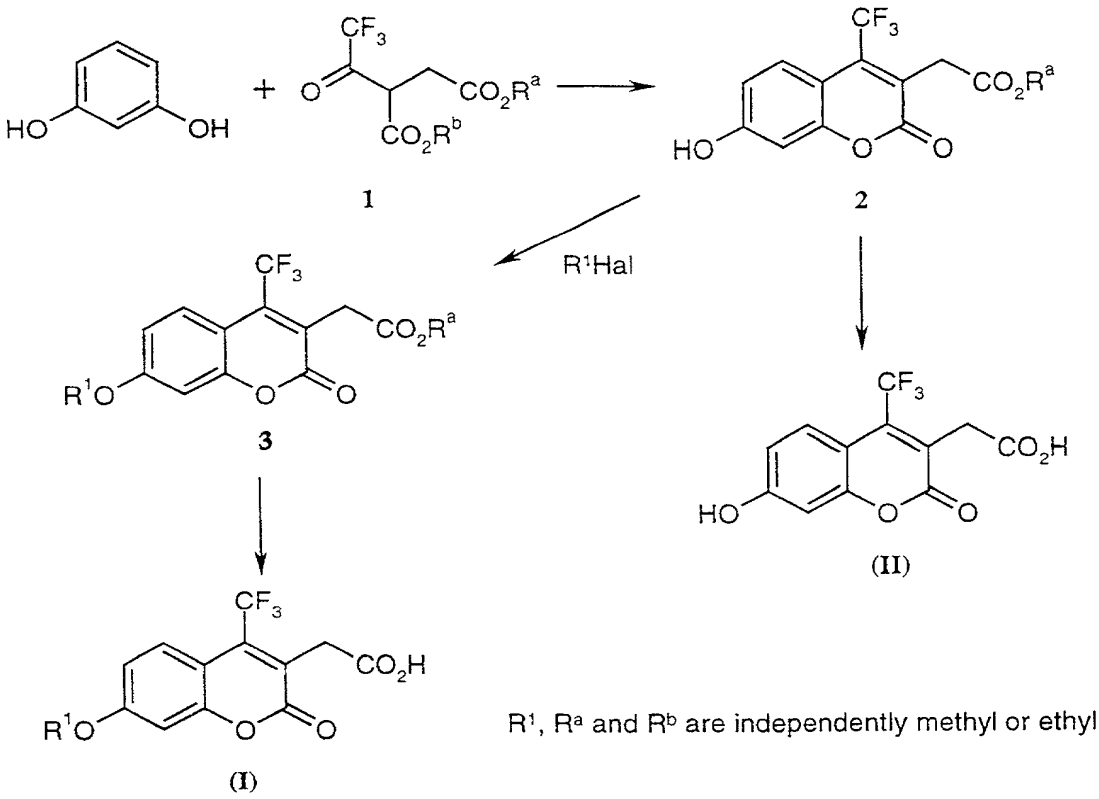
which can be scanned with suitable excitation and emission wavelengths, for example an excitation wavelength of 410 nm and an emission wavelength of 510 nm.

The assay may be carried out either in solution or utilising a solid support. When the assay is carried out in solution suitable solvents include methanol, acetonitrile and DMSO.

The test compound may be pre-incubated with enzyme prior to the addition of the substrate, or alternatively the substrate may be added simultaneously. Final concentrations of enzyme and substrate are calculated so as to achieve a suitable rate of processing for carrying out the assay. If desired, the reaction may be stopped, for example by addition of acid or solvent. The fluorescent product of formula (II) may be analysed using any conventional system of fluorescence detection, for example a multi-well plate/fluorescent plate reader.

The compounds of formula (I) and (II) are novel and as such also form part of the invention.

The compounds of formula (I) and (II) may be prepared by conventional methods, for example as shown in Scheme 1:



Scheme 1

Thus according to a further aspect of the invention there is provided a process for the production of a compound of formula (I) or (II) which comprises:

a) reaction of resorcinol and a dialkyl trifluoroacetosuccinate wherein the alkyl groups are independently selected from C_{1-2} alkyl, in the presence of polyphosphoric acid;

b) for compounds of formula (I) reaction of the resulting 7-hydroxycoumarin with a compound of formula R^1Hal, wherein R^1 is C_{1-2} alkyl and Hal is halogen e.g. iodine or bromine; and

c) ester hydrolysis to give the acid of formula (I) or (II).

The reaction of resorcinol with a dialkyl trifluoroacetosuccinate in the presence of polyphosphoric acid may suitably be performed at a temperature of about 15-30°C.

Typical reaction conditions for the alkylation of a 7-hydroxycoumarin with an alkyl halide are well known to those skilled in the art and include a solvent such as acetone at reflux in the presence of a base such as potassium carbonate.

Typical reaction conditions for ester hydrolysis are well known to those skilled in the art and include dilute hydrochloric acid in methanol or ethanol at reflux.

Dialkyl trifluoroacetosuccinates of formula **1** may be prepared from the corresponding alkyl bromoacetate and alkyl trifluoroacetoacetate according to the route described in C. Aubert *et al*, *J. Fluorine Chem.* **1989**, *44*, 361. Suitable alkyl bromoacetates and alkyl trifluoroacetoacetates are commercially available.

Since the inhibition of cytochrome P450 enzymes is often the mechanism for drug/drug interactions, the assay according to the invention is particularly useful for identifying compounds which may give rise to adverse drug/drug interactions. The assay can therefore be used in combination with the chemical modification of test compounds to increase a test compound's potential for use as a pharmaceutical.

Thus according to further aspects of the invention there are provided a method for reducing the CYP2C9 enzyme inhibitory activity of a compound, comprising the steps of identifying the compound as an inhibitor of CYP2C9 in the assay described above; and thereafter producing a chemically modified version of the test compound in which the functionality suspected to be responsible for CYP2C9 inhibition is eliminated or changed; and novel compounds produced according to this method.

The chemical modification of test compounds according to this method can be performed using techniques well known to those skilled in the art.

The novel compounds produced according to this aspect of the invention may find application as pharmaceuticals. A compound produced according to this method will be readily identifiable as novel by performing routine literature and database searches. The pharmaceutical activity of such compounds can be readily ascertained using conventional biological screening methods known to those skilled in the art.

All publications, including but not limited to patents and patent applications, cited in this specification are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference herein as though fully set forth.

The invention is illustrated by the following examples.

Example

Preparation of 7-methoxy-4-trifluoromethylcoumarin-3-acetic acid.

a) 7-Hydroxy-4-trifluoromethyl coumarin-3-acetic acid ethyl ester [**2**, R^a = Et]

Polyphosphoric acid (45 g) was added to a mixture of resorcinol (4.06 g) and diethyl trifluoroacetosuccinate (9.96 g) (Aubert, C.; Begue, J. P.; Charpentier-Morize, M.; Nee, G.; Langlois, B. *J. Fluorine Chem.* **1989**, *44*, 361). The mixture was stirred at room temperature for 24 h. Crushed ice was added and the mixture extracted with dichloromethane. The organic phase was washed with water then dried ($MgSO_4$) and evaporated. The residue was purified by chromatography on silica gel (eluent 2% methanol in dichloromethane) to give the title compound (1.24 g) m.p. 112.5 - 114.0°C. $\delta_H(CDCl_3)$ 1.30 (t, 3H), 3.96 (m, 2H), 4.24 (q, 2H), 6.66 (d, J = 2.5 Hz, 1H), 6.75 (dd, J = 9.0, 2.5 Hz, 1H), 7.55 (m, 1H); mass spectrum *m/z* 317 (MH^+).

b) 7-Methoxy-4-trifluoromethyl coumarin-3-acetic acid ethyl ester [**3**, R^1 = Me, R^a = Et]

Methyl iodide (0.41 ml) was added to a mixture of **2** (0.7 g), potassium carbonate (0.46 g) and acetone (15 ml). The mixture was heated under reflux for 5 h. After cooling the solvent was evaporated and the residue was partitioned between dichloromethane and water. The organic phase was washed with water and then dried ($MgSO_4$) and evaporated. The residue was purified by chromatography on silica gel (eluent 0.5% methanol in dichloromethane) to give the title compound (0.62 g). $\delta_H(CDCl_3)$ 1.26 (t, 3H), 3.90 (s, 3H), 3.94 (m, 2H), 4.19 (q, 2H), 6.86 (d, J = 2.6 Hz, 1H), 6.91 (dd, J = 9.2, 2.6 Hz, 1H), 7.70 (m, 1H); mass spectrum *m/z* 331 (MH^+).

c) 7-Methoxy-4-trifluoromethyl coumarin-3-acetic acid [(**I**), R^1 = Me]

A mixture of **3** (0.615 g), ethanol (5 ml) and dilute hydrochloric acid (3M, 100 ml) was heated under reflux. After 6 h the mixture was cooled and the solid collected by filtration. The dried solid was crystallised from diethyl ether/hexane to give the title compound (0.475 g) m.p. 198.5 - 200.0°C (Found: C, 51.60; H, 2.82. $C_{13}H_9F_3O_5$ requires C, 51.67; H, 3.00%); $\delta_H(CDCl_3)$ 3.90 (s, 3H), 3.94 (m, 2H), 6.87 (d, J = 2.6 Hz, 1H), 6.92 (dd J = 9.2, 2.6 Hz, 1H), 7.70 (m, 1H); mass spectrum *m/z* 325 ($M + Na^+$), 303 (MH^+), 285 ($M - OH^-$).

Assay methodology

Materials:

6.25 mM 7-Methoxy-4-trifluoromethylcoumarin-3-acetic acid (i.e. 1.88 mg/mL in DMSO)
2 % (w/v) $NaHCO_3$ - stored at approx. 4°C
50 mM potassium phosphate buffer, pH 7.4
Freshly prepared cofactor solution:- approx. the following per mL of 2 % (w/v) $NaHCO_3$
1.7 mg NADP, monosodium salt
7.8 mg glucose-6-phosphate, monosodium salt
6 Units glucose-6-phosphate dehydrogenase, Type VII from Bakers Yeast

Method:

1) Mix 1 µL 6.25 mM 7-methoxy-4-trifluoromethylcoumarin-3-acetic acid, 10 µL (100 µg) CYP2C9 microsomal protein and 209 µL buffer per incubate (giving 25 µM 7-methoxy-4-trifluoromethylcoumarin-3-acetic and 400 µg/mL protein final concentration).

2) To each well of a 96-well plate add 220 µL of incubation mix and 5 µL of test compound in methanol. (or 5 µL of appropriate solvent for control wells – methanol, acetonitrile or DMSO may be used).

3) Pre-incubate the multi-well plate in the plate reader at 37°C for 5 minutes. Pre-warm the cofactor solution at 37°C for 5 minutes.

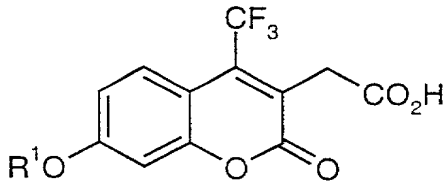
4) Add 25 µL cofactor solution to each well and scan with an excitation wavelength of 410 nm and an emission wavelength of 510 nm with a gain of 80. Scan for 10 cycles at 1 minute intervals.

Results

Confirmation of 7-methoxy-4-trifluoromethylcoumarin-3-acetic acid as a CYP2C9 substrate was achieved using sulphaphenazole, a diagnostic CYP2C9 inhibitor (Back *et al*, *British Journal of Clinical Pharmacology*, 1988, 26, 23-29). With sulphaphenazole, 7-methoxy-4-trifluoromethylcoumarin-3-acetic acid was inhibited with an IC_{50} of 0.29 μM (Figure 1), an inhibition value typical of other, well characterised, CYP2C9 substrates.

CLAIMS

1. An assay for testing for inhibitors of the enzyme CYP2C9 which comprises contacting the enzyme and a compound of formula (I):

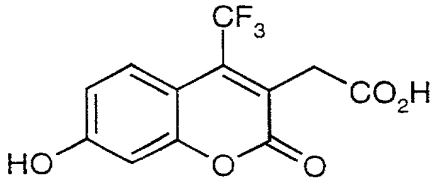


(I)

wherein R^1 represents C_{1-2}alkyl, with a test compound and measuring inhibition of O-dealkylation of the compound of formula (I) by the enzyme.

2. The assay according to claim 1 wherein R^1 is methyl.

3. The assay according to claim 1 or 2 wherein inhibition of O-dealkylation of the compound of formula (I) by the enzyme is measured by quantifying the compound of formula (II):



(II)

4. The assay according to claim 3 wherein the compound of formula (II) is quantified by fluorescence detection.

5. The assay according to claim 4 wherein the compound of formula (II) is quantified by scanning at excitation wavelength of 410 nm and an emission wavelength of 510 nm.

6. A compound of formula (I) or (II) as defined in claim 1 or 3.

7. A process for the production of a compound of formula (I) or (II) as defined in claim 1 or 3 which comprises:

a) reaction of resorcinol and a dialkyl trifluoroacetosuccinate wherein the alkyl groups are independently selected from C_{1-2} alkyl, in the presence of polyphosphoric acid;

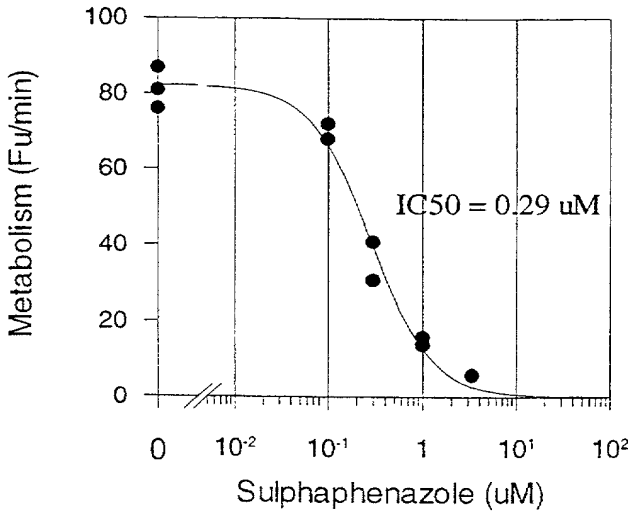
b) for compounds of formula (I) reaction of the resulting 7-hydroxycoumarin with a compound of formula R^1Hal, wherein R^1 is C_{1-2} alkyl and Hal is halogen e.g. iodine or bromine; and

c) ester hydrolysis to give the acid of formula (I) or (II).

8. A method for reducing the CYP2C9 enzyme inhibitory activity of a compound, comprising the steps of identifying the compound as an inhibitor of CYP2C9 in an assay according to any one of claims 1 to 5; and thereafter producing a chemically modified version of the test compound in which the functionality suspected to be responsible for CYP2C9 inhibition is eliminated or changed.

9. A novel compound produced according to the method of claim 8.

Figure 1: Inhibition of 7-methoxy-4-trifluoromethylcoumarin-3-acetic acid metabolism with sulphaphenazole



Docket No.: P32158 PCT/EP99/07416

DECLARATION AND POWER OF ATTORNEY

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

7-Alkoxycoumarins as CYP2C9 substrates

the specification of which (check one)

[ ] is attached hereto.

[X] was filed on 04 October 1999 as Serial No. PCT/EP99/07416
and was amended on (if applicable).

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to the patentability as defined in Title 37, Code of Federal Regulations, Section 1.56.

I hereby claim foreign priority benefits under Title 35, United States Code, Section 119(a)-(d) or Section 365(b) of any foreign application(s) for patent or inventor's certificate, or Section 365(a) of any PCT International application which designated at least one country other than the United States, listed below and have also identified below any foreign application for patent or Inventor's certificate, or PCT International application having a filing date before that of the application on which priority is claimed.

Prior Foreign Application(s)

Number	Country	Filing Date	Priority Claimed
9822140.1	GB	09 October 1998	Yes

I hereby claim the benefit under Title 35, United States Code, Section 119(e) of any United States provisional application(s) listed below.

Application Number	Filing Date

I hereby claim the benefit under Title 35, United States Code, Section 120 of any United States application(s) or Section 365(c) of any PCT International application designating the United States, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of Title 35, United States Code, Section 112, I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations, Section 1.56 which became available between the filing date of the prior application and the national or PCT international filing date of this application.

Serial No.	Filing Date	Status

I hereby appoint the practitioners associated with the Customer Number provided below to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith, and direct that all correspondence be addressed to that Customer Number:

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I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that wilful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such wilful false statements may jeopardize the validity of the application or any patent issued thereon.

1-10

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